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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
OFFICE OF BIOLOGICS RESEARCH AND REVIEW

TRANSMITTAL OF LABELS AND CIRCULARS

(Part I - Submission Of Draft And Preliminary Proof Labeling)

LABEL REVIEW NO: T2071706

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Type or print legibly in ink. Submit three copies of preliminary proofs and drafts. For revised labeling, indicate where changes have been made on the labeling copy. Assemble and staple each set, including attachments. The transmittal form must be dated and signed by the responsible head. Return both parts (1 and 2) of this form to Food and Drug Administration, Center for Drugs and Biologics, Office of Biologics Research and Review, 8800 Rockville Pike, Bethesda, Maryland 20205.

MANUFACTURER'S NAME	MERCK & CO., INC.
NAME OF PRODUCT	Measles and Rubella Virus Vaccine Live M-R-VAX II

LABELING

CHECK BELOW	TYPE SUBMITTED	REPLACES LABELING PREVIOUSLY REVIEWED REVIEW NO.	DATED	MANUFACTURER'S IDENTIFICATION NO.
	A Container Label			
	B Package Label			
X	C Circular	T1102301	10/23/91	Typed Text (768021)
	D Diluent			
	E Other (Specify)			

LABELING REPRESENTS CHANGE IN:
- ☐ Dosage
- ☐ Manufacturing Method
- ☐ Contraindications, side effects, Precautions
- ☐ Arrangement
- ☐ Wording
- ☒ Other (Specify)

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REFERENCE NUMBER

COMMENTS

See attached summary of revisions and supporting literature.

RESPONSIBLE HEAD	SIGNATURE: Wayne Rogers	DATE: 7/17/92

THE SPACE BELOW IS FOR REVIEW BY OFFICE OF BIOLOGICS RESEARCH AND REVIEW

COMMENTS

Please see the comments on the labeling and submit a revised draft

REVIEWED BY	SIGNATURE:	DATE:
RETURNED BY	SIGNATURE: Robert A Yetter	DATE: 7/22/92

FORM FDA 2567 (7/84)

PREVIOUS EDITION IS OBSOLETE.

Current Circular

Revision - CBER Letters 3/3/92, 6/8/92

AHFS Category 80:12

8880215

MSD | M-R-VAX® II
(MEASLES AND RUBELLA VIRUS VACCINE LIVE, MSD)

M R VAX® II
(Measles and Rubella Virus Vaccine Live, MSD)

DESCRIPTION

M R VAX® II (Measles and Rubella Virus Vaccine Live, MSD) is a live virus vaccine for immunization against measles (rubeola) and rubella (German measles).

M R VAX II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo and (2) MERUVAX® II (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) cultures. The vaccine viruses are the same as those used in the manufacture of ATTENUVAX (Measles Virus Vaccine Live, MSD) and MERUVAX II (Rubella Virus Vaccine Live, MSD). The two viruses are mixed before being lyophilized. The product contains no preservative.

propagated in chick embryo tissue cultures obtained from isolated Merck flocks which are specific pathogen-free.

propagated in WI-38 human diploid lung fibroblasts received from the American Type Culture Collection.

are harvested and processed as follows:

Measles

Multiple harvests of virus-containing fluids are collected, frozen and stored. The individual harvests are thawed and pooled, and stabilizer is added. The pooled vaccine is clarified by filtration, subdivided, frozen and stored at or below -60°C.

The growth medium for measles is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and human albumin) as stabilizer and neomycin.

Rubella

Multiple harvests of virus-containing fluids are collected, stabilizer is added, and the harvests are then frozen and stored at or below -60°C. The individual harvests are thawed, pooled, clarified by filtration, subdivided, frozen and stored at or below -60°C.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing human serum albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

M-R-VAX II

Frozen measles and rubella bulks are thawed, combined and diluted to the appropriate final potency. Stabilizer and buffer (phosphate) are added. The final formulated bulk is filled, frozen, lyophilized and stored at or below 8°C.

The cells, virus pools, fetal bovine serum, and human albumin are all screened for the absence of adventitious agents. Human albumin is processed using the Cohn cold ethanol fractionation procedures.

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The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ of tissue culture infectious [illegible] of the U.S. Reference Measles Virus and 1,000 $TCID_{50}$ of the U.S. [illegible] Rubella Virus [illegible] The product contains no preservative. Sorbitol and hydrolysates are added as stabilizers.

Revision - CBER Letters 3/3/92, 6/8/92

Each dose of the vaccine contains sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-R-VAX II, when reconstituted as directed, is clear yellow.

Current Circul...

Revis 1 - CBER Letters 3/3/92, 6/8/92

CLINICAL PHARMACOLOGY

Clinical studies of 237 double seronegative children, 18 months to 10 years of age, demonstrated that M-R-VAX II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95 percent and rubella HI antibodies in 99 percent of susceptible persons.

The RA 27/3 rubella strain in M-R-VAX II elicits higher immediate post vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine[1-3] and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.[10,11] The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.[11-13] The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,[11,13-15] and provide greater confidence for lasting immunity.

Measles-induced antibody levels following administration of M-R-VAX II have been shown to persist up to 11 years without substantial decline.[16,41] Continued surveillance will be necessary to determine further duration of antibody persistence.

caused by a paramyxovirus (measles virus) and a togavirus (rubella virus), respectively

pneumonia and

Measles and rubella are two common childhood viral diseases that may be associated with serious complications and/or death. For example, several types of encephalitis are caused by measles, and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1991.[41,45] For measles, 894,134 cases reported in 1941 compared to 9,488 cases reported in 1991 resulted in a 98.9% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 1,372 cases reported in 1991 resulted in a 97.6% decrease.

However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose. (see also INDICATIONS AND USAGE, Revaccination).

Efficacy of measles and rubella vaccine was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components.[48-50] These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.[57,58]

Following vaccination, antibodies associated with protection can be measured either directly by neutralization assays or indirectly by hemagglutination-inhibition (HI) or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11-13 years after primary vaccination.[16,41,51] See INDICATIONS AND USAGE, Non-Pregnant Adolescents and Adult Females, for Rubella Susceptibility Testing.

45. CDC, Summary of Notifiable Diseases, United States, 1990, MMWR 39 (53): 53-60, Oct. 4, 1991.

48. Hilleman, M.R.; Buynak, E.B.; Weibel, R.E.; et al: Development and Evaluation of the Moraten Measles Virus Vaccine, JAMA 206(3): 587-590, 1968.

49. Cutts, F.T.; Henderson, R.H.; Clements, C.J.; et al: Principles of measles control, Bull WHO 69(1): 1-7, 1991.

50. Leibhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; et al: Vaccination With RA 27/3 Rubella Vaccine, Am. J. Dis. Child. 123: 133-136, Feb. 1972.

51. Watson, J.C.; Pearson, J.A.; Erdman, D.D.; et al: An Evaluation of Measles Revaccination Among School-Entry Age Children, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #268): 143, 1991.

57. Rosen, L: Hemagglutination and Hemagglutination-Inhibiton with Measles Virus, Virology 13: 139-141, Jan 1961.

58. Brown, G.C., et. al: Fluorescent-Antibody Marker for Vaccine-Induced Rubella Antibodies, Infection and Immunity 2(4): 360-363, 1970.

Current Circular

INDICATIONS AND USAGE

~~M-R-VAX II is indicated for simultaneous immunization against measles and rubella in persons 15 months of age or older.~~ Local health jurisdictions may mandate a different vaccination schedule. (Revaccination with ~~M-R-VAX II~~ is recommended at primary or secondary school entry. See Revaccination).[17-19,26,27,53]

~~Infants who are less than 15 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin, the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 12 months of age. There is some evidence to suggest that infants immunized at less than one year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[20]~~

~~Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.~~

~~Individuals planning travel outside the United States, or who immigrate, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to international travel, individuals known to be susceptible to any or all of these diseases can receive either a single antigen vaccine (Measles, Mumps, or Rubella), or a combined antigen vaccine as appropriate. However, M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) is preferred for persons likely to be susceptible to mumps and rubella, and if a single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) regardless of their immune status to mumps or rubella.[21,22,23]~~

Revision - CBER Letters 3/3/92, 6/8/92

Primary Vaccination

M-R-VAX II is indicated for simultaneous immunization against measles and rubella in persons 15 months of age or older. Local health jurisdictions may mandate a different vaccination schedule. (Revaccination with MMR II ~~M-R-VAX II~~ is recommended at primary or secondary school entry. See Revaccination).[17-19,26,27,53]

Infants less than 15 Months of Age

Vaccination of children 6-12 months of age against measles is recommended in certain outbreak situations.[61]

Primary vaccination of infants less than 6 months of age is not recommended.

Infants first vaccinated from 6 to 12 months of age should receive ~~another dose~~ MMR at 15 months of age followed by routine vaccination at primary ~~and~~ or secondary school entry (see Revaccination).

Infants first vaccinated at 12 to 14 months of age should be revaccinated at primary or secondary school entry (see Revaccination).

receive mumps vaccine or MMR II at 15 months and should

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Non Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[*]

Women of childbearing age should be advised not to become pregnant for three months after vaccination and should be informed of the reason for the precaution.[*]

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.[**] If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to seven percent of all live births.[1] Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella immune status of vaccinees is unknown.

(see CLINICAL PHARMACOLOGY)

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia/arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

STET

Postpartum Women

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (See *Nursing Mothers*.)

Other Populations

Previously unimmunized children in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in M-R-VAX II) to reduce the risk of exposure to the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import the diseases to the United States. Therefore, ...ic to international travel, individuals known to l susceptible to one or more of these diseases c receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.[21,22,23]

Vaccination is recommended for susceptible individuals in high-risk groups such as colleg students, health-care workers, and military personnel.[53,56]

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born aft 1956 are considered susceptible and shoul be vaccinated, if there are no contraindica This includes persons who may be immune t measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with li measles vaccine on or after the first birthda

*NOTE The Immunization Practices Advisory Committee (ACIP) has recommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others."[38]

**NOTE The Immunization Practices Advisory Committee (ACIP) has stated "When practical and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella. However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."[38]

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Revaccination Children first vaccinated when younger than 12 months of age should be revaccinated at 15 months of age followed by revaccination as described below.

Infants first vaccinated at 12 to 14 months of age should be revaccinated at primary school entry.

Revaccination with M-R-VAX II is recommended at primary or secondary school entry. Revaccination may sereconvert primary failures or boost antibody titers of those individuals whose titers have declined.

The American Academy of Pediatrics (AAP), the Immunization Practices Advisory Committee (ACIP), and some state and local health agencies have recommended guidelines for routine revaccination and to help control outbreaks.[26,27]

A primary difference among these recommendations is the timing of revaccination: the ACIP recommends routine revaccination at entry into kindergarten or first grade, whereas the AAP recommends routine revaccination at entrance to middle school or junior high school. In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.[26,27]

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Post-Exposure Vaccination

Vaccination of individuals exposed to natural measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before exposure, substantial protection may be afforded.[53,54,55] There is no conclusive evidence that vaccination of individuals recently exposed to natural rubella will provide protection.[56]

53. Recommendations of the Immunization Practices Advisory Committee (ACIP), Measles Prevention, MMWR 38(S-9): 1-13, December 29, 1989.

54. King, G.E.; Markowitz, L.E.; Patriarca, P.A.; et al: Clinical Efficacy of Measles Vaccine During the 1990 Measles Epidemic, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #1286): 313, 1991.

55. Krasinski, K.: Borkowsky, W.: Measles and Measles Immunity in Children Infected With Human Immunodeficiency Virus, JAMA 261(17): 2512-2516, 1989.

56. Recommendations of the Immunization Practices Advisory Committee (ACIP), Rubella Prevention, MMWR 39 (RR-15): 1-18, November 23, 1990.

Revision - CBER Letters 3/3/92, 6/8/92

MMR II

Revaccination

Children first vaccinated when younger than 12 months of age should receive another dose at 15 months of age followed by revaccination as described below.

Infants first vaccinated at 12 to 14 months of age should be revaccinated at primary or secondary school entry.

Revaccination with M-R-VAX II is recommended at primary or secondary school entry. Revaccination may sereconvert primary failures or boost antibody titers of those individuals whose titers have declined.

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Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

receive mumps vaccine or MMR II at 15 months and should

Post-Exposure Vaccination

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Current Circular

Use with other Vaccines

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and M-R-VAX II.

M-R-VAX II should not be given less than one month before or after administration of other virus vaccines.

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See PRECAUTIONS, Drug Interactions

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CONTRAINDICATIONS

...not give M-R VAX II to pregnant females, the possible effects of ...accine on fetal development are unknown at this time. If vaccina... of postpubertal females is undertaken, pregnancy should be ...voided for three months following vaccination (See PRECAUTIONS, Pregnancy.)

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin)

~~A history of anaphylactic or anaphylactoid reactions to eggs (see HY...~~

~~HYPERSENSITIVITY TO EGGS below)~~

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses, [42] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated [see PRECAUTIONS].

Hypersensitivity to any component of the vaccine.

, although mild respiratory infection without fever is not a contraindication for vaccination.

Please delete reference to HIV infected individuals from CONTRAINDICATIONS and discuss under PRECAUTIONS

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,42

42. Recommendations of the Immunization Practices Advisory Committee (ACIP), General Recommendations on Immunization, ~~MMWR~~ 38(13): 205-228, April 7, 1989.

Please move to PRECAUTIONS →

*NOTE: The Immunization Practices Advisory Committee (ACIP) has stated that "M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) should be considered for all symptomatic HIV-infected children, including children with acquired immunodeficiency syndrome (AIDS)". However, these patients may not respond to vaccination, and the safety of such usage has not been established.

Please reword e.g. "limited data are available ..."

WARNINGS

Due caution should be employed in administration of M-R-VAX II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

~~HYPERSENSITIVITY TO EGGS~~

Live measles vaccine is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.[39]

Hypersensitivity to Eggs

may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The American Academy of Pediatrics recommends skin testing prior to vaccination for persons with a history of anaphylactic reactions to egg ingestion.[43] The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).[44]

43. Peter, G.; et al. (eds): Report of the Committee on Infectious Diseases, Twenty-second Edition, American Academy of Pediatrics, 1991, pp. 29-30.

44. Isaacs, D.; Menser, M.: Modern Vaccines. Measles, Mumps, Rubella, and Varicella, Lancet 335: 1384-1387, June 9, 1990.

Current Circular

Revision - CBER Letters 3/3/92, 6/8/92

PRECAUTIONS

[redacted]

injection (1:1000)

If there is a family history of congenital or hereditary immunodeficiency, the immune status of the patient should be determined and confirmed to be normal prior to vaccination.

~~(see CONTRAINDICATIONS for patients with overt clinical manifestations)~~ delete

~~(human)~~.

As for any vaccine, vaccination with M-R-VAX II may not result in protection in 100% of vaccinees.

- please delete this phrase or reword to be consistent with current AAP & ACIP recommendations.

Care should be taken by the health-care provider for the safe and effective use of the product.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Do not keep the vaccine (before and after reconstitution) at temperatures above 8°C (40°F) during use or when stored (see HOW SUPPLIED, Storage).

M-M-R II should not be injected into a blood vessel.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Needles used for vaccination should not be recapped and should be disposed of properly.

Information For Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent or guardian.

The health-care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS).

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.[52]

Pregnancy should be avoided for three months following vaccination.

Laboratory Tests

See INDICATIONS AND USAGE, Non-Pregnant Adolescents and Adult Females, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

52. Vaccine Adverse Event Reporting System - United States, MMWR 39(41): 730-733, Oct. 19, 1990.

Current Version

Revision

Drug Interactions

Use With Other Vaccines

M-R-VAX II should not be given less than one month before or after administration of other live viral virus vaccines.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. For example, the American Academy of Pediatrics has noted that when the patient may not return, some practitioners prefer to administer DTP, OPV, and M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) on a single day. If done, separate sites and syringes should be used for DTP and M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live).[89] The Immunization Practices Advisory Committee (ACIP) recommends routine simultaneous administration of M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), DTP and OPV or inactivated polio vaccine (IPV) to all children ≥15 months who are eligible to receive these vaccines on the basis that there are equivalent antibody responses and no clinically significant increases in the frequency of adverse events when DTP, M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) and OPV or IPV are administered either simultaneously at different sites or separately.* Administration of M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) at 15 months followed by DTP and OPV (or IPV) at 18 months remains an acceptable alternative, especially for children with caregivers known to be generally compliant with other health-care recommendations.[42]

Please include a statement about simultaneous use with H. influenzae type b vaccine.

Recommendations of the Immunization Practices Advisory Committee (ACIP), General Recommendations or Immunization, MMWR 38(13): 205-228, April 7, 1989.

53. Recommendations of the Immunization Practices Advisory Committee (ACIP), Measles Prevention, MMWR 38(S-9): 1-13, December 29, 1989.

56. Recommendations of the Immunization Practices Advisory Committee (ACIP), Rubella Prevention, MMWR 39 (RR-15): 1-18, November 23, 1990.

*NOTE: The Immunization Practices Advisory Committee (ACIP) recommends administering M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) concomitantly with the fourth dose of DTP and the third dose of OPV to children 15 months of age or older providing that 6 months have elapsed since DTP-3; or, if fewer than three DTPs have been received, at least 6 weeks have elapsed since the last dose of DTP and OPV.

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delete.

Immunosuppressive Therapy

The immune status of patients about to und immunosuppressive therapy should be evaluated that the physician can consider whether vaccination prior to the initiation of treatment is indicated. (see CONTRAINDICATIONS and PRECAUTIONS).

The Immunization Practices Advisory Committee (ACIP) has stated "that patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live-virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g., nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of measles, mumps or rubella vaccine."[59,61]

The ACIP also notes "that replication of vaccine viruses can be enhanced in persons with immune-deficiency diseases and in persons with immunosuppression, as occurs with leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, large doses of corticosteroids. For this reas patients with such conditions or therapies (except patients with symptomatic infection with human immunodeficiency virus [HIV] ~~(however, see CONTRAINDICATIONS)~~) should not be given live measles, mumps or rubella virus vaccine."[59,61]

Immune Globulin

Administration of immune globulins concurrently with ~~M-M-R~~ II (Measles, Mumps, and Rubella Virus Vaccine Live) may interfere with the expected immune response.[53,56]

See also PRECAUTIONS, General.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

M-R-VAX II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

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Pregnancy

Pregnancy Category C

[redacted]nal reproduction studies have not been conducted with [redacted]X II. It is also not known whether M-R VAX II can cause fetal [redacted]when administered to a pregnant woman or can affect reproduc-[redacted]capacity. Therefore, the vaccine should not be administered to pregnant females, furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10 year survey involving over 7000 pregnant women who received rubella vaccine within 3 months before or after conception, (of whom 100 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome;[1] (2) Reports have indicated that contracting of natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast fed infants.[2] In the infants with serological evidence of rubella infection, none exhibited severe disease, however, one exhibited mild clinical illness typical of acquired rubella.[2,3] Caution should be exercised when M-R VAX II is administered to a nursing woman.

Pediatric Use

M-R-VAX II is recommended for simulta immunization against measles and rubella persons 15 months of age and older. See INDICATIONS AND USAGE for use in infants 15 months of age.

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ADVERSE REACTIONS

Burning and/or stinging of short duration at the injection site have been reported.

The adverse clinical reactions associated with the use of M-R-VAX II are those expected to follow administration of the monovalent vaccines given separately. These may include malaise, sore throat, cough, rhinitis, headache, dizziness, fever, rash, nausea, vomiting or diarrhea, mild local reactions such as erythema, induration, tenderness and regional lymphadenopathy, thrombocytopenia and purpura, allergic reactions such as wheal and flare at the injection site or urticaria, polyneuritis, and arthralgia and/or arthritis usually transient and rarely chronic.

Anaphylaxis and anaphylactoid reactions have been reported.

Vasculitis has been reported rarely.

Moderate fever (101 - 102.9°F [38.3 - 39.4°C]) occurs occasionally, and high fever (above 103°F [39.4°C]) occurs less commonly. On rare occasions, children developing fever may exhibit febrile convulsions. Afebrile convulsions or seizures have occurred rarely following vaccination with live attenuated measles vaccine. Syncope, particularly at the time of mass vaccination, has been reported. Rash occurs infrequently and is usually minimal, but rarely may be generalized. Erythema multiforme has also been reported rarely.

Forms of optic neuritis, including retrobulbar neuritis, papillitis, and retinitis may infrequently follow viral infections, and have been reported to occur 1 to 3 weeks following inoculation with some live virus vaccines.

Clinical experience with live attenuated measles and rubella virus vaccines given individually indicates that encephalitis and other nervous system reactions have occurred very rarely. These might occur also with M-R-VAX II.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine very rarely.[37] In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per two thousand reported cases).

There have been rare reports of ocular palsies, Guillain-Barré syndrome, or ataxia occurring after immunization with vaccines containing live attenuated measles virus. The ocular palsies have occurred approximately 3-24 days following vaccination. No definite causal relationship has been established between these events and vaccination. Isolated reports of polyneuropathy including Guillain-Barré syndrome have also been reported after immunization with rubella containing vaccines.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with natural measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Center for Disease Control suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.[38]

Local reactions characterized by marked swelling, redness and vesiculation at the injection site of attenuated live measles-virus vaccines, and systemic reactions including atypical measles, have occurred in persons who received killed-measles vaccine previously. M-R-VAX II was not given under this condition in clinical trials. Rarely, more severe reactions that required hospitalization, including prolonged high fevers and extensive local reactions, have been reported.[39] Panniculitis has been reported rarely following administration of measles vaccine.[40]

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of natural rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia have also been reported following administration of MERUVAX II (Rubella Virus Vaccine Live, MSD).

Chronic arthritis has been associated with natural rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0.3%, women: 12-26%)[41,46,47], and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (36-45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

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The following adverse reactions are listed in decreasing order of frequency within each category and have been reported during clinical trials or with use of the marketed vaccine:

Body as a Whole

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site.

Fever; headache; malaise; panniculitis; atypical measles; syncope; dizziness.

Cardiovascular System

Vasculitis.

Digestive System

Vomiting; diarrhea; nausea.

Hemic and Lymphatic System

Regional lymphadenopathy; thrombocytopenia; purpura; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm.

Musculoskeletal System

Arthralgia; arthritis; myalgia.

Nervous System

Febrile convulsions; ataxia; paresthesia; encephalitis; encephalopathy; Subacute Sclerosing Panencephalitis (SSPE); Guillain-Barre Syndrome (GBS); polyneuropathy; afebrile convulsions or seizures; ocular palsies; polyneuritis.

Respiratory System

Cough; rhinitis; sore throat.

Skin

Rash; urticaria; Stevens-Johnson Syndrome; erythema multiforme.

Special Senses - Ear

Otitis media; nerve deafness.

Special Senses - Eye

Optic neuritis; retrobulbar neuritis; papillitis; retinitis; conjunctivitis.

46. Gershon, A., et al: Live attenuated rubella virus vaccine: comparison of responses to HPV-77-DE5 and RA 27/3 strains, Am. J. Med. Sci. 279(2): 95-97, 1980.

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Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.[52] A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

The table and footnotes may be deleted

Table 1
Reportable Events Following Vaccination

Vaccine	Event	Interval From Vaccination
Measles, Mumps and Rubella	A. Anaphylaxis or anaphylactic shock	24 hours
	B. Encephalopathy (or encephalitis)*	15 days
	C. Residual seizure disorder*	*
	D. Any acute complication or sequela (including death) of above events	no limit
	~~E. see CONTRAINDICATIONS~~	

*Events listed are required by law to be reported to the U.S Department of Health and Human Services; however, VAERS will accept all reports of suspected adverse events after the administration of any vaccine

Guide to interpretation:

- Shock-collapse or hypotonic-hyporesponsive collapse may be evidenced by signs or symptoms such as decrease in or loss of muscle tone, paralysis (partial or complete), hemiplegia, hemiparesis, loss of color or change of color to pale white or blue, unresponsiveness to environmental stimuli, depression of or loss of consciousness, prolonged sleeping with difficulty arousing, or cardiovascular or respiratory arrest.
- Residual seizure disorder may be considered to have occurred if no other seizure or convulsion unaccompanied by fever or accompanied by a fever of <102 F occurred before the first seizure or convulsion after the administration of the vaccine involved.
  AND, if in the case of measles-, mumps-, or rubella-containing vaccines, the first seizure or convulsion occurred within 15 days after vaccination OR in the case of any other vaccine, the first seizure or convulsion occurred within 3 days after vaccination.
  AND, if two or more seizures or convulsions unaccompanied by fever or accompanied by a fever of <102 F occurred within 1 year after vaccination
- The terms seizure and convulsion include grand mal, petit mal, absence, myoclonic, tonic-clonic, and focal motor seizures and signs
- Encephalopathy means any substantial acquired abnormality of, injury to, or impairment of brain function. Among the frequent manifestations of encephalopathy are focal and diffuse neurologic signs, increased intracranial pressure, or changes lasting >6 hours in level of consciousness, with or without convulsions. The neurologic signs and symptoms of encephalopathy may be temporary with complete recovery, or they may result in various degrees of permanent impairment. Signs and symptoms such as high-pitched and unusual screaming, persistent unconsolable crying, and bulging fontanel are compatible with an encephalopathy, but in and of themselves are not conclusive evidence of encephalopathy. Encephalopathy usually can be documented by slow wave activity on an electroencephalogram

52. Vaccine Adverse Event Reporting System - United States, MMWR 39(41): 730-733, Oct. 19, 1990.

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DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dosage of vaccine is the same for all persons. Inject the total volume of the single-dose vial (about 0.5 mL) or 0.5 mL of the multiple dose vial of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune globulin concurrently with* M-R-VAX II

During shipment, to assure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store M-R-VAX II at 2 - 8°C (36 - 46°F). *Protect from light.*

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 Dose Vial (available only to government agencies/institutions) — Withdraw the entire contents (7 mL) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 Dose Vial (available only to government agencies/institutions) — Withdraw the entire contents (30 mL) of diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

Each dose contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. *Reference Measles Virus* and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. M-R-VAX II, when reconstituted, is clear yellow.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer t of the upper arm.

The customary age for primary vaccination is 15 months. MMR II

Revaccination with ~~M-R-VAX II~~ is recommended at primary or secondary school entry. See also INDICATIONS AND USAGE, Revaccination.

Children first vaccinated when younger than 1 months of age should receive ~~another dose~~ at 15 months of age. See also INDICATIONS AND USAGE, Revaccination. MMR II

Immune Globulin (IG) is not to be given concurrently with M-R-VAX II

If the lyophilized vaccine cannot be dissolved, discard.

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whenever solution and container permit.

Use With Other Vaccines

See PRECAUTIONS, Drug Interactions, Use With Other Vaccines

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HOW SUPPLIED

[illegible] 4751 — M-R-VAX II is supplied as a single-dose vial of lyophilized [illegible]ine, NDC 0006-4751-00, and a vial of diluent

[illegible]. 4677/4300 — M-R-VAX II is supplied as follows: (1) a box of 10 [illegible]le-dose vials of lyophilized vaccine (package A), NDC 0006-4677-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature (6505-01-088-8004, Ten Pack).

Available only to government agencies/institutions:

No. 4678 — M-R-VAX II is supplied as one 10 dose vial of lyophilized vaccine, NDC 0006-4678-00, and one 7 mL vial of diluent.

No. 4679 — M-R-VAX II is supplied as one 50 dose vial of lyophilized vaccine, NDC 0006-4679-00, and one 30 mL vial of diluent (6505-01-088-8095, 50 Dose)

Storage

~~It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (36-46°F) and discard if not used within 8 hours.~~

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During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Protect the vaccine from light at all times, since such exposure may inactivate the virus.

Before reconstitution, store the vial of lyophilized vaccine at 2-8°C (36-46°F) or below. The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (36-46°F) and discard if not used within 8 hours.

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